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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,499	12/11/2001	Kevin P. Baker	39780-2830.42 US	6886

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/015,499	BAKER ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. ___.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/18/07 has been entered.

2. Applicant's arguments filed 1/18/07 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 28-35 & 38-40 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility, for the reasons made of record in Paper No: 20040913 & 20050428, and as follows.

Applicant's arguments on pages 6-18 of the response have been fully considered but are not found to be persuasive because the specification still does not identify a single "reasonable use" for the claimed *polypeptides* of the instant invention, because no "in general [consensus exists for] gene amplification increases mRNA expression" reasonably exists in the art, nor "in general, [is] there a [reasonable] correlation between mRNA levels and polypeptide levels", for

the reasons previously made of record. In other words, even though "the present specification... discloses... evidence that ***the gene*** encoding the PRO1788 polypeptide is ... amplified in colon tumors [emphasis added]", the claimed functional use of "wherein the nucleic acid... is amplified..." for detecting colon tumors is not equivalent to identifying a use for PRO1788 mRNA, nor for extrapolating a use for the *claimed PRO1788 polypeptides* that are transcribed from PRO1788 mRNA, which further possess no known and distinguishable assayable activity. Likewise, as previously made of record, "increase in gene copy number" (i.e., DNA data) is not equivalent to increased mRNA levels, which are not equivalent to increased polypeptide levels. Moreover, not a single submitted declaration has looked at PRO1788 mRNA and especially at PRO1788 polypeptide levels, which would be useful in establishing a *specific* utility for the instant invention. The Polakis II and Scott Declarations under 37 CFR 1.132, filed 11 August 2006, are further insufficient to overcome the rejection of claims 28-35 & 38-40 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the same reasons previously made of record, as it relates to the teachings of Haynes et al. (analyzing 80 genes/proteins), Hu et al. (analyzing 2286 genes), Chen et al. (analyzing 165 protein blots), Pennica et al., and Konopka et al.

In particular, the Polakis II Declaration is not deemed persuasive, because the issue is not that approximately 200 gene transcripts (i.e., mRNA) have been identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, or that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 90% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. The issue is that the instant specification provides no

information regarding increased mRNA levels of PRO1788, or increased PRO1788 polypeptide levels, in tumor samples relevant to normal samples. Only gene amplification (DNA) data is presented within the instant specification. Importantly, it is noted that this declaration further does not provide data for the Examiner to independently draw any conclusions. Only Dr. Polakis' conclusions/ "opinions" are provided in this declaration. Likewise, no evidence is presented to support Dr. Polakis' statement that "in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." No such dogma is universally recognized within the art; especially as it relates to small changes in gene expression being predictive of cancer. Simply put, gene amplification (i.e., as it relates to the instant specification) is not equivalent to gene expression (i.e., mRNA), which is not the same as polypeptide data (i.e., as claimed).

Secondly, the Scott Declaration is directed to "DNA microarray analysis", which is not on point with that claimed (i.e., PRO1788 polypeptides). Importantly, it is further noted that this declaration also does not provide data for the Examiner to independently draw any conclusions. Only Declarant Scott's conclusions/ "opinions" are provided in this declaration. Nevertheless, Scott does state that "direct measurement of protein expression levels remains non-trival", which is the issue directly related to this rejection. In other words, only assertions that "DNA microarray analysis" is useful are provided within the Scott Declaration. In contrast, both the instant specification and all of the currently submitted declarations fail to provide any information/data regarding increased polypeptide levels of PRO1788 in tumor samples relevant to normal samples. Therefore, no use for the claimed *polypeptides* related to SEQ ID NO: 397 still currently exists, and thus, no *specific* utility exists, by definition.

Additionally, as previously made of record, a utility of being a diagnostic target for colon tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use, because amplification of DNA in colon tumors is not the same as showing PRO1788 causes colon cancer, and because it is not known whether PRO1788 is expressed in corresponding normal colon tissues, or what the relative levels of expression are, or whether PRO1788 is merely involved in colon tissue becoming colon tissue, due to its increased expression. All that the specification does is invite the artisan to determine the significance of this "gene amplification". This is not a *substantial utility*, by definition. Moreover, Polaski's conclusion that "it is a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein", and that "in general, there is a correlation between mRNA levels and polypeptide levels", is contradicted by the teachings of Pennica et al., who alternatively teach that although "*WISP-2* DNA was amplified in *colon tumors*, ... its *mRNA expression* was [conversely] significantly *reduced in the majority of tumors*... [emphasis added]", and additionally contradicted by the teachings of Konopka et al. previously made of record, whom also demonstrated a lack of correlation between gene amplification and increased polypeptide levels.

Lastly, as extensively made of record, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided sufficient information for one to reasonably assess a "real world" use for the instant invention without discovering such after-the-fact (i.e., as it relates to establishing a *substantial* utility).

In summary, and in contrast to Applicants' interpretation of the data of Chen et al., Hu et al., Haynes et al., and Pennica et al., the issue remains that the specification fails to provide any evidence on whether or not the PRO1788 polypeptide levels are also increased in these tumor samples. Again, note that Example 143 in the instant specification describes gene amplification assay data, which is well known in the art to measure DNA levels, and not polypeptide levels. Because the instant claims are directed to PRO1788 *polypeptides*, it is, therefore, imperative to find evidence in the relevant scientific art as to whether or not a small increase in DNA levels would be considered by the skilled artisan to be predictive of increased in subsequent polypeptide levels. Given the evidence provided by Haynes et al., Hu et al. and Chen et al., who further look at multiple genes, it is clear that one skilled in the art would not assume that gene amplification "more likely than not" would result in significantly increased polypeptide levels. Thus, "*more likely than not*" no generalized correlation exists between DNA amplification resulting in mRNA overexpression, which then results in a subsequent increase in polypeptide levels, and for the reasons previously made of record.

As previously made of record, Chen et al further drives home this point on page 304 (right column) by their description of the state of the art in that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-translational mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of protein present in a given cell or tissue". Likewise, in contrast to Applicants arguments on pages 9-10 of the response, Lewin alternatively acknowledges that "control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein...".

Futcher even further drives home this issue in their statement that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (pg. 7397,col. 1, 1st pp). As also previously made of record, neither Orntoft, Hyman, Pollack, Bea nor Godbout show a "general" mRNA/protein correlation, for the reasons previously made of record. In fact, none of the other "118 references" (with duplicate citations of Abstracts) look at DNA/protein correlations. In particular, neither Hyman nor Pollack looked at polypeptide levels, in which Hyman further stated that less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Thus, Applicants' arguments remain not on point with the fact situation in the instant case, and therefore, remain not persuasive, because gene expression data alone (i.e., DNA; as it relates to the instant specification) is not equivalent to mRNA data, which is not equivalent to polypeptide data, in contrast to Applicants' assertions. It is again pointed out that Applicants have also previously acknowledged that "the correlation between mRNA and protein level is not exact" (see page 17 of the response), and therefore, cannot be "more likely than not true", by definition.

In conclusion, for the reasons discussed above and previously made of record, because the proposed use of the PRO1788 polypeptides are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides, the instant claims have no specific nor substantial utility, consistent with that held by the court in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966):

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

5. Claims 28-35 & 38-40 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for the reasons made of record in Paper NOs: 20040913 & 20050428.

6. Claims 28-33 & 39-40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper NOs: 20040913 & 20050428, and as follows.

It is noted that Applicants did not argue against the written description rejection made of record.

In summary, a recitation related to "wherein the nucleic acid... is amplified..." does not reasonably constitute a "functional limitation" for the claimed polypeptides. The specification has further not described or shown possession of polypeptides 80-99% homologous to SEQ ID NO: 397, which retain the function of SEQ ID NO: 397, if later discovered. Nor have Applicants described a representative number of species that have 80-99% homology to SEQ ID NO: 397, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 397; consistent with that held by the court in *Vas-Cath Inc. v. Mahurkar* previously made of record.

As previously made of record, page 301 of the specification specifically states that "[t]he PRO polypeptides described herein *may be isolated from a variety of sources*, such as from human tissue types *or from another source*... [emphasis added]" . In contrast, the sole single *human* polypeptide species described is PRO1788 of SEQ ID NO: 397. No written description is provided in the specification for any other species of PRO1788 molecules, in which disclosure of a single *"human"* polypeptide sequence does not reasonably constitute "the claimed genus of polypeptides". Therefore, Applicants are clearly not in compliance with the written description requirement under 35 U.S.C. 112, first paragraph, for the reasons made of record, which are consistent with that held by the courts in *Fiers v. Revel*, *Fiddes v. Baird*, and *Univ. California v. Eli Lilly and Co.*, previously made of record. See again MPEP 2163.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
April 10, 2007

ROBERT C. HAYES, PH.D.
PRIMARY EXAMINER